Cognitive function, disease burden and the structural connectome in systemic lupus erythematosus

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METHODS

Image processing

Each 3D T_1-weighted volume was parcellated into 85 regions-of-interest (ROI), consisting of 68 cortical (34 per hemisphere) and 16 sub-cortical (eight per hemisphere) regions, plus the brain stem, using the Desikan-Killiany atlas in FreeSurfer (http://surfer.nmr.mgh.harvard.edu). The results of the segmentation procedure were then used to construct grey and white matter masks for use in network construction and to constrain the tractography output. Using tools provided by the FDT package in FSL (http://fsl.fmrib.ox.ac.uk/fsl), the dMRI data were pre-processed to reduce systematic imaging distortions and bulk subject motion artifacts by affine registration of all subsequent EP volumes to the first T_2-weighted EP volume[1]. Skull stripping and brain extraction were performed on the registered T_2- and diffusion-weighted EP volumes and applied to the fractional anisotropy (FA) volume calculated by DTIFIT in each subject[2]. The neuroanatomical ROIs determined by FreeSurfer were then aligned from 3D T_1-weighted volume to diffusion space using a cross-modal nonlinear registration method. As a first step, linear registration was used to initialize the alignment of each brain-extracted FA volume to the corresponding FreeSurfer extracted 3D T_1-weighted brain volume using a mutual information cost function and an affine transform with 12 degrees of freedom[1]. Following this initialization, a nonlinear deformation field based method (FNIRT) was used to refine local alignment[3]. FreeSurfer segmentations and anatomical labels were then aligned to diffusion space using nearest neighbour interpolation.

Tractography

Whole-brain probabilistic tractography was performed using FSL's BedpostX/ProbTrackX algorithm[4]. Probability density functions, which describe the uncertainty in the principal directions of water molecule diffusion, were computed with a two-fibre model per voxel[4]. Streamlines were then constructed by sampling from these distributions during tracking using 100 Markov Chain Monte Carlo iterations with a fixed step size of 0.5 mm between successive points. Tracking was initiated from all white matter voxels and streamlines were constructed in two collinear directions until terminated by the following stopping criteria designed to minimize the amount of anatomically implausible streamlines: (i) exceeding a curvature threshold of 70 degrees; (ii) entering a voxel with FA below 0.1; (iii) entering an extra-cerebral voxel; (iv) exceeding 200 mm in length; and (v) exceeding a distance ratio metric of 10. The distance ratio metric[5], excludes implausibly tortuous streamlines.

Network construction

FA-weighted networks were constructed by recording the mean FA value along streamlines connecting all ROI (network node) pairs. The endpoint of a streamline was considered to be the first grey matter ROI encountered when tracking from the seed location. Self-connections were removed, and if no streamlines were found between a pair of nodes, the corresponding matrix entry was set to zero. Across the cohort, only connections which occurred in at least two-thirds of subjects were retained[6]. Finally, for each FA-weighted connectivity matrix, five global network measures, plus *mean edge weight* (mean FA for the network), were computed using the brain connectivity toolbox (https://sites.google.com/site/bctnet), namely, network density (fraction of present connections to all possible connections), strength (average sum of weights per node), mean shortest path length between nodes, global efficiency (average inverse shortest path length in the network) and clustering coefficient (fraction of triangles around a node). Mean shortest path length is inversely related to the other connectivity metrics.

Identification of hubs

Network hubs[7], described as regions with a large number of connections, were identified by taking the average connectivity matrix for the cohort and creating a hub score based on betweeness centrality and degree for each of the 85 cortical and sub-cortical regions identified by FreeSurfer. These regions were then ranked on the hub score with the top 20% identified as network hubs.

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